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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,307	11/22/2004	Pieter Hendrik Pouwels	GRT/117-509	9841

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
TONGUE, LAKIA J	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,307	POUWELS ET AL.	
	Examiner	Art Unit	
	Lakia J. Tongue	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-39* is/are pending in the application.

4a) Of the above claim(s) *9-18,21-32 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/28/04; 10/12/04; 1/5/05; 1/17/07.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I claims 1-18 and 33-39 with a further election of *Lactobacillus acidophilus* in the reply filed on March 13, 2007 is acknowledged.

The traversal is on the ground that:

1) The examination of all pending claims would not constitute a serious burden.

2) The pending claims are generic for *Lactobacillus acidophilus* and thus, all *Lactobacillus* species should be examined for the generic claims.

3) The claimed subject matter is not anticipated by Blaser et al. Rather than disclosing the internal insertion of a heterologous polypeptide, Blaser et al. disclose the replacement of an internal fragment of SapA by foreign sequences.

The above-mentioned arguments have been considered and found persuasive.

With regard to Point 1, MPEP § 808.02 recites that for the purposes of the initial requirement of a restriction, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02. The inventions above are patentably distinct. The search for each of the above inventions would not be co-extensive in scope particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity,

enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application.

With regard to Point 2, Groups I, IV and V read on patentably distinct modified bacterium, which are patentably distinct because they are drawn to bacterium that are different and distinct species.

With regard to Point 3, while Blaser et al. do not anticipate the special technical feature of the amended claims, the special technical feature does not contribute to the art as exemplified by Smit et al. (U.S. Patent 5,500,353). Smit et al. disclose a bacterium having an s-layer modified that the bacterium S-layer protein gene contains one or more in-frame sequences coding for one or more heterologous polypeptides. Moreover, Smit et al. disclose that the practitioner will choose an appropriate region (or specific amino acid position) of the S-layer for insertion of a desired polypeptide (see abstract and column 4, lines 63-65). Lastly, Smit et al. disclose that the S-protein layer is a two-dimensional crystalline array (see column 7, lines 63-64).

The requirement is still deemed proper and is therefore made FINAL.

Therefore, claims 1-18 and 21-39 are pending. Claims 1-9, 12-15, 18, 21-25, and 31 have been amended. Claims 33-39 have been added. Claims 19-20 have been canceled. Claims 9-18, 21-32, and 35-39 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1-8, 33 and 34 are currently under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on June 28, 2004, October 12, 2004, June 5, 2005 and January 17, 2007 are in compliance with the provisions of 37 CFR 1.97 and has been considered. An initialed copy is attached hereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-8, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to a modified bacterial surface layer protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said protein is able to crystallize.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is

known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CRFC1988). The Wands factors have been considered in the establishment of this scope of enablement rejection. These factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to a modified bacterial surface layer protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize.

Breadth of the claims: The claims encompass any and all bacterial surface layer proteins, comprising any internal insertion of any heterologous polypeptide, wherein said modified protein is able to crystallize.

Direction or guidance presented in the specification: The specification does not provide substantive evidence that the claimed composition is capable of crystallizing. The specification is silent with regard to which bacterial surface layer protein will crystallize when the modification comprises any internal insertion of a heterologous polypeptide. The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The amino acid sequence of a protein determines its structural and functional properties, predictability of which internal insertion will result in certain activity, which is very complex, is well outside the realm of routine experimentation. Accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, and thus the specification needs to provide an enabling disclosure.

Lastly, Applicant has failed to "fully characterize" the polypeptide that are capable of crystallizing when any internal insertion of any heterologous polypeptide is made. The specification does not describe with any degree of specificity which bacterial surface layer protein is to be used or at what point the internal insertion of a heterologous polypeptide is to be made, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Presence or absence of working examples: There are no working examples, provided to rectify the missing information in the instant specification pertaining to the claimed variant.

State of the prior art: protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Accordingly, it follows that the functional domains associated with a given function can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of protective immunity,

the specification, as filed, does not provide enablement for immunogenic compositions capable of adjuvanting a specific immune response.

Quantity of experimentation necessary: The quantity of experimentation necessary would be undue as no relevant evidence has been made of record establishing the amount of experimentation necessary. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidence by the state of the prior art, attempting the construct and test variants of the claimed invention would constitute undue experimentation.

4. Claims 1-8, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to a modified bacterial surface layer protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus of polypeptides or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention. In the instant case, to fulfill the written description requirement, a representative number of S-proteins with inserted heterologous proteins that can still crystallize need to be described. Specifically, the specification needs to provide guidance as to which heterologous peptides/proteins can be inserted at a given position within a given S-protein and not affect crystallization.

A representative number of species means that the species that are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus.

Moreover, the skilled artisan cannot envision the detailed chemical structure of the claimed polypeptides. The claims encompass a genus of polypeptides which are not adequately described. The recitation of any modified bacterial surface layer protein (indicating any protein) comprising the internal insertion, which is non-specific, represents a partial structure and the genus as claimed is highly variable. The specification fails to provide any additional representative species of the claimed genus to show that Applicant was in possession of the claimed genus. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential ability to bind a specific biological agent. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the

inventor] invented what is claimed."). Thus, an Applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 6 is rendered vague and indefinite by the use of the term "pl". It is unclear what is meant by said term, as it is not explicitly defined in the specification. What constitutes "pl"? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim 7 is rendered vague and indefinite by the use of the phrase "antigen causing or specific for a disease". It is unclear what is meant by said term, as it is not explicitly defined in the specification. What constitutes "antigen causing or specific for a disease"? As written, it is impossible to determine the metes and bounds of the claimed invention.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J. Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
6/7/07

ROBERT A. ZEMAN
PRIMARY EXAMINER